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GB 2048710A
GB 2030559A
GB 2020181A
GB 1517879
GB 1516442
GB 1511614
GB 1425550
GB 1417527
GB 1366796
EP 0009410A
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(54) **Rod-like Moulded Drug**

(57) The present invention relates to a molded drug comprising a mixture of a high-molecular material absorbable in the living body and a medicine which drug is in the form of rods substantially capable of piercing the living body. The moulded drug is to be pierced in an affected part of the living body of a patient suffering from, for example, cancer, whereby the medicine is gradually released to kill the cancer cells.

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SPECIFICATION

New Molded Drug

The present invention relates to a new rod-shaped drug substantially capable of being pierced in a living body as a whole. An object of the present invention is to provide a new drug delivery system for drugs to be applied locally to an affected part of patient.

Recently, studies are made intensively on an administration method in which a drug is given continuously to an affected part or around the part of a patient having local tumor or cancer for a long period of time. For the controlled-release administration by the local application of a drug, there have been known various methods such as a method wherein capsules containing a drug are embedded around an affected part, a method wherein a drug is shaped into tablets or pellets using an excipient such as a resin, if necessary, and they are embedded around an affected part a method wherein a drug is treated with a capsule-forming agent by a process known *per se*, the thus obtained micro-capsules containing the drug are injected in a muscle or blood vessel around an affected part so that the capsules stay in the capillary vessels near the affected part to allow the drug to exude from the capsules.

However, the embedding around an affected part requires a surgical operation and parts in which the embedding is possible are limited. When powders or pellets molded by using an excipient are made fluid and directly injected in the body by means of, for example, an injector, it is difficult to deeply embed them in the affected part, though the surgical operation is not required. An essential defect of the micro-capsule method has been pointed out that the micro-capsules staying in a blood vessel inevitably inhibit the blood circulation resulting in necrosis around it. Defects of both methods are that a capsule-forming material or fixing polymer material remains in the body. The high-molecular material remaining in the body for a long period of time would exert some influences on the living body.

After intensive investigations on new administration methods of drugs made under these circumstances, the inventors have attained to the present invention.

A term "high-molecular material absorbable in living body" herein indicates a high-molecular material which is decomposed under vital conditions in the body, such as enzymes and body temperature or combination of many other factors occurring in the body, into metabolites which are harmless to the living body and which are absorbed in the living body or excreted therefrom by functions peculiar to the living body. Those high-molecular materials may be chemically synthesized or they may be obtained from materials occurring in living bodies or they may be a combination thereof.

As the chemically synthesized high-molecular materials, there may be mentioned, for example, polyglycolic acid, polylactic acid, glycolic acid/lactic acid copolymer and compositions comprising them as well as polyalkyl cyanoacrylates. As the materials occurring in living bodies, there may be mentioned, for example, soluble collagen and oxidized cellulose. They may be used also in the form of a mixture thereof. However, high-molecular materials which are synthesized completely chemically and which are absorbable in a living body are desirable for shaping them into rods capable of being pierced in the living body to attain the characteristic feature of the present invention.

Particularly preferred materials are aliphatic polyesters. It has been known that those esters are absorbed in the living body in a harmless form or excreted. Polyglycolic acid and polylactic acid have a high compression strength and, therefore, even if they are molded into needle-shaped rods, they still have a stength sufficient for the piercing into the body. Rods having a compression strength sufficient for the piercing in the living body can be obtained from the glycolic acid/lactic acid copolymer by selecting glycolic acid/lactic acid ratio in the copolymer according to the size of the rods. In glycolic acid homopolymers and copolymers, glycolic acid content is preferably 100—80 wt. %. In lactic acid homopolymers and copolymers, lactic acid content is preferably 100—90 wt. %. As the polyglycolic acid, those having a low polymerization degree and an intrinsic viscosity of about 0.2 (determined in a solution comprising 7 parts by weight of trichlorophenol and 10 parts by weight of phenol at 30°C) are usable. From the viewpoint of the molding operation, those having an intrinsic viscosity of up to 0.9 are preferred. The lactic acid homopolymers and copolymers have a degree of crystallinity of preferably at least 30% in the form of rods.

The drugs used in the present invention are preferably those which can directly be applied to parts around the affected part such as carcinostatics, hormones, insulin, local analgesics and antibiotics.

The carcinostatics used in the present invention include antimetabolites such as 5-FU, THFU and cytarabine, alkylating agents such as carmustine and nimumstine (nidran), and anticarcinogenic antibiotics such as mitomycin, carzinophilin, adriamycin and bleomycin.

As other medical administration systems in which the rods of the present invention are used, there may be mentioned local anesthesia and X-ray projection. Anesthetics and contrast media used in those systems are also included in the present invention. Further, other drugs may be used in the present invention without any particular limitation.

Ratio of the high-molecular material absorbable in the living body to the drug in the molded composition according to the present invention is preferably 30—99 parts by weight to 70—1 part by weight. The ratio is determined depending on active ingredient-releasing rate required, dose, period

and size and strength of the molded composition of the present invention and also according to purpose of the administration.

The present invention provides a molded carcinostatic drug of controlled release type which comprises 1—70 wt. %, based on an aliphatic polyester absorbable in the living body, of a carcinostatic agent and which is to be pierced in a part affected by cancer. The rod-shaped carcinostatic drug of controlled release type capable of being pierced directly in the body is obtained by selecting an aliphatic polyester which is harmless to the living body and decomposed and absorbed in the living body and has excellent physical properties, particularly a high compression strength as the high-molecular material for fixing the drug and also specifically selecting the drug content of the molded product.

For obtaining the rod-shaped drug substantially capable of piercing into the living body without using any plunger according to the present invention, for example, cylindrical rods having a diameter of about 1.5—2 mm should have a compression strength of preferably at least 200 g when the length in 1 cm.

The present invention is characterized in that a mixture of the high-molecular material absorbable in the living body and the medicine is molded into rods capable of piercing in the body. The term "rods substantially capable of piercing into the living body" herein indicates rods including needle-like rods having a diameter of up to about 2 mm and rods obtained by cutting a molded plate of a given thickness into rods of a suitable width of up to about 5 mm according to a width of the affected part in which they are to be inserted. A preferred shape of the rods is a needle-like shape. If necessary, an end of each rod may be sharpened so that it can be pierced around or in an affected part directly or by means of a plunger or the like in the same manner as in the acupuncture and moxibustion. When the needle-like molded product having a diameter of up to 2 mm is to be produced, it is desirable to select polyglycolic acid having a quite high compression strength as the high-molecular material absorbable in the living body. According to the period in which the active ingredient is to be released gradually and amount of the active ingredient, a combination of rods having different diameters and lengths may be employed or plates having different thicknesses and lengths selected may be cut into the rods.

The length of the rods varies depending on the affected part in which they are to be pierced. Rods to be pierced in organs in the body have lengths ranging from about 1 cm to about 5 cm (toothpick-shaped rods).

The molded drugs of the present invention may be obtained by various ordinary methods of molding high-molecular materials. The method is selected suitably depending on the purpose to form rods or plates. For example, the method is suitably selected from melt spinning, compression molding, injection molding, transfer molding, casting and sintering molding methods. The drug is mixed with the high-molecular material absorbable in the living body by melting at a temperature below a decomposition temperature of the drug or the drug is mixed with said high-molecular material dissolved in a solvent and the mixture is then molded. If a high-molecular monomer easily polymerizable into the high-molecular material absorbable in the living body can be used for the production of the molded drug, the high-molecular monomer is mixed with the drug, and then the mixture is charged in a mold to carry out the polymerization by a proper polymerization-initiation method to obtain the intended molded drug. However, the method wherein a solvent is used in the molding step or the method wherein a monomer is polymerized to obtain a molded product is not preferred, since the removal of the solvent from the molded drug or the removal of the unreacted monomer is difficult. In order to distribute the active ingredient uniformly in the high-molecular base absorbable in the living body, it is desirable to homogeneously mix the active ingredient powder with the powder base before the melting by heating.

The drug thus molded into rods contains the high-molecular material which is absorbable in the living body and which has a relatively high compression molding and it does not always require the use of a plunger such as an injector or surgical operation for the piercing. The rods can be administered to an affected part of patient accurately and easily substantially without causing bleeding. Accordingly, the active ingredient in a high concentration acts on the affected part in only a limited area. Particularly in case the surgical operation is impossible in the treatment of cancers in the organs such as a liver, the rod-shaped drug of the present invention can be pierced therein to effect the therapy. If a small amount of X-ray contrast medium is incorporated in the drug in addition to a carcinostatic or the like, it is possible to confirm the cite of the piercing according to roentgenoscopy at the time of the administration. Further, the dose can be maintained or controlled in a deep, affected part by previously determining the active ingredient content of the rod and concentration thereof to be gradually released, since the drug of the present invention is molded into rods having uniform shape and a given active ingredient content. The following examples will illustrate the present invention.

Example 1

100 parts by weight of glycolic acid/lactic acid polymer (50:50) passed through a 60 mesh sieve was mixed homogeneously with 50 parts by weight of finely pulverized 5-fluorouracil (a product of Mitsui Seiyaku Co.) to obtain a composition. The composition was molded into rods having a diameter of 1 mm by means of a Koka type flow tester (a product of Shimazu Seisakusho) at 180°C.

The molded product having a length of 1 cm had a compression strength in the longitudinal direction of 320 g.

Example 2

100 parts of polyethyl cyanoacrylate obtained by polymerizing ethyl cyanoacrylate monomer commercially available as an adhesive for the surgical operation by casting in a petri dish was dissolved in 1000 parts by weight of acetone. 50 parts by weight of finely pulverized 50 fluorouracil was dispersed in the solution and the whole was poured in a petri dish to obtain a plate by casting method.

The plate was dried at 100°C in vacuum for 24 hours to completely remove acetone therefrom. The thus obtained plate having a thickness of 0.1 mm was cut into rods. The rods had a compression strength of 270 g, when determined in the same manner as in Example 1.

Example 3

100 parts by weight of polyglycolic acid (having an intrinsic viscosity in a mixed solution of 7 parts by weight of trichlorophenol and 10 parts by weight of phenol at 30°C of 0.3) passed through a 60 mesh sieve was mixed with 30 parts by weight of finely pulverized 5-fluorouracil in a constant temperature bath at 210°C to obtain a solution. Rods having a diameter of 1 mm were prepared from the solution by the crystal pulling method.

The rods had a compression strength in the longitudinal direction of 750 g/cm.

Example 4

100 parts of ethyl cyanoacrylate monomer was mixed with 30 parts of 5-fluorouracil. The mixture was poured in a glass petri dish at room temperature to obtain a plate having a thickness of 1 mm comprising polyethyl cyanoacrylate and 5-fluorourcil. The plate was cut into rods having a diameter of 1 mm. The rods having a length of 1 cm had a compression strength in the longitudinal direction of 640 g.

Example 5

30 parts by weight of polyglycolic acid (the same as that used in Example 3) was mixed with 70 parts by weight of glycolic acid/lactic acid copolymer (50:50; the same as that used in Example 1). The mixture was dissolved in a solution of resin in chloroform. A chemical shown in Table 1 was added to the resulting solution and the whole was poured in a needle-shaped mold. The solvent was vaporized to obtain needle-shaped molded product having a diameter of 2 mm. It had a compression strength in the longitudinal direction (1 cm length) as shown in Table 1.

Table 1

Active ingredient	*Amount (in total 50 mg)*	*Compression strength of the molded product*
1-(2-Tetrahydrofuryl)-5-fluorourcil (carcinostatic)	15 mg	740 g
Mitomycin C (carcinostatic)	15 mg	750 g
Ilosone (carcinostatic)	20 mg	250 g

Example 6

100 parts by weight of polyglycolic acid (having an intrinsic viscosity in a mixed solution of 7 parts by weight of trichlorophenol and 10 parts by weight of phenol at 30°C of 0.3) passed through a 60 mesh sieve was mixed homogeneously with 30 parts by weight of finely pulverized 5-fluorourcil. The mixture was treated in a constant temperature bath at 210°C to obtain a solution. Rods having a diameter of 1 mm were prepared from the solution by the crystal pulling method.

The rods having a length of 1 cm had a compression strength in the longitudinal direction of 750 g.

Example 7

100 parts by weight of glycolic acid/lactic acid copolymer (comprising 80 wt. % of glycolic acid and 20 wt. % of lactic acid) passed through a 60 mesh sieve was homogeneously mixed with 50 parts by weight of finely pulverized mitomycin (a product of Sankyo Co.). The mixture was molded into rods having a diameter of 1 mm by means of a Koka type flow tester (a product of Shimazu Seisakusho) at 180°C.

The rods had a compression strength in the longitudinal direction of 380 g as determined by using samples having a length of 1 cm.

Test 1

A controlled release effect of 5-fluorourcil rods prepared using polyglycolic acid in Example 6 was examined.

The needle-shaped drug having a length of 1 cm and a diameter of 2 mm (total weight: 50 mg, 5-fluorourcil content: 16.5 mg) was pierced and completely embedded in the liver of a rat (body weight: 385 g, 100 days after the birth). Change in amount of 5-fluorourcil remaining in the polymer base with time was examined to determine the exudation rate of 5-fluorourcil.

The results are shown in Table 1.

Table 1

Time (days)	*Amount of 5-phlorouracil remaining (mg)*	*Rate (%)*
1	10.73	65
3	6.11	37
5	3.79	23
7	1.82	11
11	0.49	3
15	0	0

Thus, it was recognized that 5-fluorourcil was released gradually over 15 days.

5-fluorourcil concentration in the serum of the rat was as low as 0.2—0.02 μg/g for 7 days directly after the embedding. It is supposed that the active ingredient in a high concentration acts only on and around an affected part without causing any side effect.

Test 2

Yoshida sarcoma cells were planted in the abdomen of each of two rats weighing 296 g and 340 g, respectively. Two weeks thereafter, a rod containing 5-fluorourcil (having a length of 1 cm, diameter of 1.5 mm, total weight of 20 mg and 5-fluorourcil content of 6.0 mg) obtained by using polyglycolic acid in Example 6 was pierced and embedded in each rat and advance of sarcoma was observed.

The results are shown in Table 2.

Table 2

Rat No.	*Condition of rat before the administration*	*Change after the administration*				
		4 days	*8 days*	*11 days*	*13 days*	*20 days*
I	296 g (15×15 mm)	303 (18×14)	315 (14×10)	330 (6×6)	332 (0)	360 (0)
II	340 g (12×22 mm)	340 (15×15)	359 (14×14)	364 (11×11)	376 (6×6)	402 (0)

Numerals in the parentheses represent sarcoma diameters.

It is recognized that the disease was completely cured 13 days after the administration of the molded drug of the present invention.

Claims

1. A molded drug comprising a mixture of a high-molecular material absorbable in the living body and a medicine which drug is molded into rods substantially capable of piercing in the living body.

2. A molded drug according to Claim 1 wherein the high-molecular material absorbable in the living body is one or more materials selected from the group consisting of polyglycolic acid, polylactic acid, glycollc acid/lactic acid copolymer and polyalkyl cyanoacrylates.

3. A molded drug according to Claim 1 wherein the medicine is that usable for the local administration to an affected part.

4. A molded drug according to Claim 1 wherein the medicine is a carcinostatic medicine.

5. A molded drug according to Claim 1 wherein the rod has a compression strength of at least 200 g when the diameter is 1.5—2 mm and the length is 1 cm.

6. A molded carcinostatic of controlled release type according to Claims 1 to 5 which contains 1—70 wt. %, based on an aliphatic polyester (selected from the group consisting of polyglycolic acid, polyactic acid, and glycolic acid/lactic acid copolymer), of a carcinostatic agent and which has been molded into rods to be pierced in an affected part in the body.

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